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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/009,897	12/14/2001	Shingo Kato	Q 67685	4572

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EXAMINER	
GOLDBERG, JEANINE ANNE	
ART UNIT	PAPER NUMBER
1634	

DATE MAILED: 02/01/2005

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/009,897	KATO ET AL.	
	Examiner	Art Unit	
	Jeanine A Goldberg	1634	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *28 October 2004*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-20* is/are pending in the application.

4a) Of the above claim(s) *13,17,18 and 20* is/are withdrawn from consideration.

5)☐ Claim(s) *11 and 19* is/are allowed.

6)☒ Claim(s) *1-10,12 and 14-16* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date *1/05*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

1. This action is in response to the papers filed October 28, 2004. Currently, claims 1-20 are pending. Claims 13, 17-18, 20 have been withdrawn as drawn to non-elected subject matter.

2. All arguments have been thoroughly reviewed but are deemed non-persuasive for the reasons which follow. This action is made FINAL.

3. Any objections and rejections not reiterated below are hereby withdrawn.

4. This action contains new grounds of rejection necessitated by amendment.

Election/Restrictions

5. Restriction is required under 35 U.S.C. 121 and 372.

This application contains the following inventions or groups of inventions which are not so linked as to form a single general inventive concept under PCT Rule 13.1.

In accordance with 37 CFR 1.499, applicant is required, in reply to this action, to elect a single invention to which the claims must be restricted.

Group I, claim(s) 1-17, drawn to methods of determining HIV-1 subtypes by amplifying a portion of the env gene of HIV-1.

Group II, claim(s) 18, drawn to a kit comprising primer pairs.

6. The inventions listed as Groups I-II do not relate to a single general inventive concept under PCT Rule 13.1 because, under PCT Rule 13.2, they lack the same or corresponding special technical features for the following reasons.

According to PCT Rule 13.2, unity of invention exists only when there is a shared same or corresponding special technical feature is a contribution over the prior art. The inventions listed in Group I do not relate to a single general inventive concept because the lack of the same or corresponding special technical feature. The technical feature of Group I is "the env gene of HIV-1" which is shown by Korber et al (Human Retroviruses and AIDS 1992) to lack novelty or inventive step and does not make it a contribution over the prior art.

Applicant is required to select a single combination of primers for examination. The combination may require a single pair or a combination comprising all possible pairs.

7. During a telephone conversation with Gordon Kit on May 30, 2003 a provisional election was made with traverse to prosecute the invention of Group I, primers of SEQ ID NO: 20 and 28 directed to subtype B, claims 1-12, 14-16. Affirmation of this election must be made by applicant in replying to this Office action. Claims 13, 17-18 are withdrawn from further consideration by the examiner, 37 CFR 1.142(b), as being drawn to a non-elected invention.

8. Applicant is reminded that upon the cancellation of claims to a non-elected invention, the inventorship must be amended in compliance with 37 CFR 1.48(b) if one or more of the currently named inventors is no longer an inventor of at least one claim remaining in the application. Any amendment of inventorship must be accompanied by a request under 37 CFR 1.48(b) and by the fee required under 37 CFR 1.17(i).

Response to Arguments

The response traverses the restriction. The response asserts that "if the method of Claim 1 is found allowable, the corresponding kits of Claim 18 will *almost certainly* be allowable as well." This argument has been thoroughly reviewed, but is not found persuasive because this application was filed as a 371 and thus a lack of unity is appropriate. As set forth above, there is no special technical feature because the prior art teaches the env gene. Moreover, a search for the primers and a search for the methods are not coextensive.

With respect to rejoinder, where applicant elects claims directed to the product, and a product claim is subsequently found allowable, withdrawn process claims that depend from or otherwise include all the limitations of the allowable product claim will be rejoined in

accordance with the provisions of MPEP § 821.04. **Process claims that depend from or otherwise include all the limitations of the patentable product** will be entered as a matter of right if the amendment is presented prior to final rejection or allowance, whichever is earlier. Amendments submitted after final rejection are governed by 37 CFR 1.116; amendments submitted after allowance are governed by 37 CFR 1.312. Rejoinder is not appropriate for this application since applicant did not elect claims direct to the product.

The response requests that "the Examiner expand the search to include the entire subject matter of Claim 1, since the elected species has not found in the prior art." The generic Claim 1, has been examined and has been found non-allowable. Additional species will not be searched, since there is not allowable generic claim. Upon the allowance of the linking claim(s), the restriction requirement as to the linked inventions shall be withdrawn and any claim(s) depending from or otherwise including all the limitations of the allowable linking claim(s) will be entitled to examination in the instant application. Applicant(s) are advised that if any such claim(s) depending from or including all the limitations of the allowable linking claim(s) is/are presented in a continuation or divisional application, the claims of the continuation or divisional application may be subject to provisional statutory and/or nonstatutory double patenting rejections over the claims of the instant application. Where a restriction requirement is withdrawn, the provisions of 35 U.S.C. 121 are no longer applicable. *In re Ziegler*, 44 F.2d 1211, 1215, 170 USPQ 129, 131-32 (CCPA 1971). See also MPEP § 804.01.

Thus for the reasons above and those already of record, the restriction is maintained.

Priority

9. This application claims priority to Japanese documents 11/167736 and 2000/23581. It is noted that no translation of these documents has been filed.

Should applicant desire to obtain the benefit of foreign priority under 35 U.S.C. 119(a)-(d) prior to declaration of an interference, a translation of the foreign application should be submitted under 37 CFR 1.55 in reply to this action.

The certified copies of the Japanese documents are presented as artifacts in the instant application.

Maintained Rejections

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

10. This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the

applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

11. Claims 1-7, 12, 14 are rejected under 35 U.S.C. 103(a) as being unpatentable over Barbosa et al (Tranfus. Sci. Vol. 19, No. 1, pages 39-43, 1998) in view of Wang et al (US PgPub 2002/0106639, August 2002) and Korber Human Retroviruses and AIDS (1992 and 1997) and Hogan (US Pat. 5,595,874, Jan 1997).

Barbosa et al. (herein referred to as Barbosa) teaches a method of distinguishing between HIV-1 subtypes (A to I) using PCR and heteroduplex mobility. Barbosa teaches PCR amplification of HIV-1 env gene regions. Barbosa teaches that the method is able to distinguish between individual strains and may also provide reliable information for phylogenetic analysis (page 40, col. 1). Barbosa teaches using the env gene comprising the C2 and C3 region. The PCR primers used are directed to various regions of the env gene. It is noted positions 7001-7020 are the same regions identified by Delwart et al. (Methods : A companion to Methods in Enzymology, Vol. 12, pages 348-354, 1997) using ED7 primer (page 350) which is SEQ ID NO: 20.

Barbosa does not specifically teach a method for determining HIV-1 subtypes which relies upon different pairs or primers for different HIV-1 subtypes.

However, Wang et al (US PgPub 2002/0106639, August 2002) teaches methods of detecting subtypes of PCV using a comparison alignment of PCV1 and PCVII. The multiplex PCR assay used for the detection of PCV identified and distinguished between the presence of the two isolates PCVI and PCVII. (see Figure 5 and 6)(para 30 and 31). A comparison between the viral genomes indicates that the genomes share approximately 76% identity (para 79). For the multiplex primers, two primers were designed to identify the

PCV group-specific sequences and strain-specific sequences (para 168). Example 6 illustrates multiplex PCR in PCVII identification. Wang teaches that "in order to differentiate the two strains of porcine circoviruses, PCVI and PCVII, two sets of primers were designed based upon the comparative analysis of the viral DNA sequences" (para 194).

Further, both Korber 1992 and Korber 1997 teach HIV genomic sequences from various subtypes of the env gene. The 1992 alignment provides a "consensus" sequence for Subtype A, B, C, D, E, O. The 1997 alignment provides more information over the genomic sequence. Each of these sequences comprises SEQ ID NO: 20.

However, Hogan et al. (herein referred to as Hogan) teaches a method of preparing nucleic acids for assays which allow for distinguishing organisms. Hogan teaches that "we can confidently design probes based on a few rRNA sequences which differ between the target organism and its phylogenetically closest relatives" (col. 6, lines 35-45). Hogan teaches the use of specific primers col. 6-7, lines 50-67, lines 1-12, and furthermore provides specific guidance for the selection of primers,

> "Once the variable regions are identified, the sequences are aligned to reveal areas of maximum homology or 'match'. At this point, the sequences are examined to identify potential probe regions. Two important objectives in designing a probe are to maximize homology to the target sequence(s) (greater than 90% homology is recommended) and to minimize homology to non-target sequence(s) (less than 90% homology to non-targets is recommended). We have identified the following useful guidelines for designing probes with the desired characteristics.
> First, probes should be positioned so as to minimize the stability of the probe:nontarget nucleic acid hybrid. This may be accomplished by minimizing the length of perfect complementarity to non-target organisms, avoiding G and C rich regions of homology to non-target sequences, and by positioning the probe to span as many destabilizing mismatches as possible (for example, dG:rU base pairs are less destabilizing than some others). Second, the stability of the probe:target nucleic acid hybrid should be maximized. This may be accomplished by avoiding long A and T rich sequences, by terminating the hybrids with G:C base pairs and by designing the probe with an appropriate Tm. The beginning and end points of the probe should be chosen so that the length and %G and %C result in a Tm about 2-10°C higher than the temperature at which the final assay will be performed. The

> importance and effect of various assay conditions will be explained further herein. Third, regions of the rRNA which are known to form strong structures inhibitory to hybridization are less preferred. Finally, probes with extensive self complementarity should be avoided."

Therefore, it would have been prima facie obvious to one of ordinary skill at the time the invention was made to have modified the methods of Barbosa directed to distinguishing between HIV-1 subtypes with the method of Wang who uses multiplexing with two sets of primers specific to particular subtypes to distinguish two viral genomic sequences. The art teaches the important to distinguish between HIV-1 subtypes A-I for reliable genetic screening as well as for phylogenetic analysis, see Barbosa. The ordinary artisan would have recognized the art demonstrated methods for distinguishing between subtypes and isolates. The art teaches multiplex methods for distinguishing between viral genome isolates which includes using primer pairs specific to the distinct isolates. The ordinary artisan would have been motivated to have used the multiplex method of Wang for the expected benefits of multiplex methods which include saving on reagents, utilizing less sample and efficiency. Since two primer pairs are combined into a single assay, the assay requires less reagents, utilizes less sample and requires less technician time for preparation. Thus, the ordinary artisan would have been motivated to have developed a multiplex PCR assay for distinguishing two or more viral genomic sequences from HIV-1 for example. The art provides alignment comparisons between HIV subtypes (see Korber). Thus, the ordinary artisan would have been motivated to have designed primers for the multiplex amplification "in order to differentiate" the strains, subtypes or isolates of HIV-1. Hogan provides specific teachings how to differentiate between regions of interest and non-interest. Designing probes and primers to know aligned regions for differentiation of

subtypes was routine in the art at the time the invention was made. Hogan provides particular guidelines to selecting probes and primers which may be used to detect a particular target at the exclusion of all other targets. The ordinary artisan would have been motivated to have generated primer pairs for the multiplex method of Wang using the primer design guidelines of Hogan. Barbosa teaches using the env gene comprising the C2 and C3 region. Therefore, the ordinary artisan would have been motivated to have targeted the known region for distinguishing subtypes of HIV-1. Furthermore, the ordinary artisan would have been motivated to have chosen a nucleic acid control which was present in all subtypes and universal to HIV-1 to ensure the positive control existed to ensure the effectiveness of the amplification. Hogan teaches determining primers to regions which are conserved among multiple subtypes and isolates. Therefore, designing a positive control to ensure the fidelity of the assay would have been obvious to the ordinary artisan at the time the invention was made.

Response to Arguments

The response traverses the rejection. The response asserts that "Barbosa, Delwart, Hahn provide evidence that there was a long-felt need for a non-labor intensive method of determining HIV-1 subtype or genetic make-up of an HIV-1 population" (Page 19 of response filed October 28, 2004). This argument has been reviewed but is not convincing because the instant response does not appear to meet the standard needed to prove long-felt need and failure of others as provided by 716.04. First, MPEP 716.01(c) makes clear that "The arguments of counsel cannot take the place of evidence in the record. In re Schulze , 346 F.2d 600, 602, 145 USPQ 716, 718 (CCPA 1965). Examples of attorney statements which are not evidence and which must be supported by an appropriate affidavit

or declaration include statements regarding unexpected results, commercial success, solution of a long - felt need, inoperability of the prior art, invention before the date of the reference, and allegations that the author(s) of the prior art derived the disclosed subject matter from the applicant." Here, the statements regarding the long-felt need must be supported by evidence, not argument.

MPEP 716.04 specifically sets forth the requirements necessary for long-felt need. Establishing long-felt need requires objective evidence that an art recognized problem existed in the art for a long period of time without solution. The relevance of long-felt need and the failure of others to the issue of obviousness depends on several factors. First, the need must have been a persistent one that was recognized by those of ordinary skill in the art. In re Gershon, 372 F.2d 535, 539, 152 USPQ 602, 605 (CCPA 1967) ("Since the alleged problem in this case was first recognized by appellants, and others apparently have not yet become aware of its existence, it goes without saying that there could not possibly be any evidence of either a long felt need in the . . . art for a solution to a problem of dubious existence or failure of others skilled in the art who unsuccessfully attempted to solve a problem of which they were not aware."); Orthopedic Equipment Co., Inc. v. All Orthopedic Appliances, Inc., 707 F.2d 1376, 217 USPQ 1281 (Fed. Cir. 1983) (Although the claimed invention achieved the desirable result of reducing inventories, there was no evidence of any prior unsuccessful attempts to do so.).

Second, the long-felt need must not have been satisfied by another before the invention by applicant. Newell Companies v. Kenney Mfg. Co., 864 F.2d 757, 768, 9 USPQ2d 1417, 1426 (Fed. Cir. 1988) (Although at one time there was a long-felt need for a "do- it-yourself" window shade material which was adjustable without the use of tools, a

prior art product fulfilled the need by using a scored plastic material which could be torn. "[O]nce another supplied the key element, there was no long-felt need or, indeed, a problem to be solved".)

Third, the invention must in fact satisfy the long-felt need. In re Cavanagh, 436 F.2d 491, 168 USPQ 466 (CCPA 1971).

The response asserts that Barbosa states that serological tests are frequently inconclusive , methods to distinguish HIV-1 subtypes are needed. The response further asserts that Hahn wises to analyzed genetic variation; and Delwart proposes DNA heteroduplex assay to estimate degree of genetic variation between two isolates. The response concludes that the present invention is not obvious over the cited art, because, although non-labor intensive methods of determining HIV-1 subtype were critically needed, and given that PCR (a non labor intensive method) was well-known technique as of the priority date of this application, no reliable method for determining HIV-1 subtype using PCR had been successful. This argument has been thoroughly reviewed, but is not found persuasive because the prior art, as exemplified by Engelbracht, does teach a method which involves PCR (a non-labor intensive method) to detect HIV-1 subtypes. Furthermore, the response fails to establish that an art recognized problem existed in the art for a long period of time without solution. The response fails to identify any attempts by the art, with failures, for designing non-labor intensive methods or methods for detecting subtypes, without solution. The prior art, has infact overcome the immunological problems provided by Barbosa, with nucleic acid detection methods, as identified by the response, namely Delwart and Hahn and additional Engelbrecht. The non-obviousness of the instant invention is not overcome in view of the arguments provided.

Thus for the reasons above and those already of record, the rejection is maintained.

New Grounds of Rejection Necessitated by Amendment

12. Claims 8-10, 12, 15-16 are rejected under 35 U.S.C. 103(a) as being unpatentable over Barbosa et al (Tranfus. Sci. Vol. 19, No. 1, pages 39-43, 1998) in view of Wang et al (US PgPub 2002/0106639, August 2002) and Korber Human Retroviruses and AIDS (1992 and 1997) and Hogan (US Pat. 5,595,874, Jan 1997) as applied to Claims 1-7, 12, 14 above and further in view of Zazzi et al. (J. Med. Virology, Vol. 38, pages 172-174, 1992).

Neither Barbosa, Wang, Korber, or Hogan specifically teach using nested PCR for detection of HIV-1 type DNA.

However, Zazzi et al. (herein referred to as Zazzi) teaches nested PCR for detection of HIV-I DNA in clinical specimens. Zazzi teaches a highly sensitive two-step PCR method was evaluated for detection of HIV-1. The product resulting from the first amplification reaction is used as the template for the second PCR with an internal (nested) primer pair. Zazzi teahes that the two step amplification protocol is simple and rapid and fulfills the requirements of sensitivity and specificity for use in a clinical laboratory (abstract).

Therefore, it would have been prima facie obvious to one of ordinary skill at the time the invention was made to have modified the PCR method of Barbosa, Wang, Korber, or Hogan to include nested PCR for the expected benefits taught by Zazzi. Zazzi specifically teaches the benefits of the nested or two step amplification over single amplification. The ordinary artisan would have been motivated to have modified the method to obtain a more sensitive and specific method using nested PCR as taught by Zazzi.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

13. Claims 1-3, 14 are rejected under 35 U.S.C. 102(b) as being anticipated by Engelbrecht et al. (J. of Virological Methods, Vol. 55, pages 391-400, 1995).

The claims have been amended to broaden the scope of the claims. The claims no longer require that the target sequence of an HIV-1 env gene is different at the 5' or 3' terminal nucleotide depending on the HIV-1 subtype. The claims have been broadened to require amplification to obtain a product and detection of the product to determine subtype.

Engelbrecht et al. (herein referred to as Engelbrecht) teaches a method of detection of S. African HIV-1 subtypes by PCR and hybridization. Engelbrecht teaches using PCR with env primer pairs. HIV-1 samples from patients with AIDS or ACR were analyzed. The env gene of 22 virus strains was sequences. Engelbrecht teaches primer pairs for env region, namely SK68 /Sk69. The PCR products were detected by probe hybridization (page 395). Hybridization with DIG oligonucleotide labeled probes was carried out on filters. Engelbrecht teaches "with the env primer pair, profile d detected 100 proviral genome copies but failed to detect many of the C-subtypes and one B-subtype" (page 397). As seen in Figure 1, the fragment sizes range from 104-592 (limitations of Claim 2). The oligo probe (SK70) used, belongs to subtype B, with ensuing weak hybridization reactions with lo level subtype C amplicons (page 397).

While Claim 1 states that the amplification product is indicative of one of four HIV-1 substypes, it is unclear how this limitation contributes to the active process of amplification and detection. Moreover, the terminal region of the amplification product is, inherently, 1-30 nucleotides in length. The claim does not appear to require any particular limitations for this terminal region. Moreover, at this region, variation between the subtypes exists, therefore, the terminal region would differ. Therefore, Engelbrecht broadly teaches the claimed method required by the instant claims.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

14. Claims 8, 15-16 are rejected under 35 U.S.C. 103(a) as being unpatentable over Engelbrecht et al. (J. of Virological Methods, Vol. 55, pages 391-400, 1995) in view of Zazzi et al. (J. Med. Virology, Vol. 38, pages 172-174, 1992).

The claims have been amended to broaden the scope of the claims. The claims no longer require that the target sequence of an HIV-1 env gene is different at the 5' or 3' terminal nucleotide depending on the HIV-1 subtype. The claims have been broadened to require amplification to obtain a product and detection of the product to determine subtype.

Engelbrecht et al. (herein referred to as Engelbrecht) teaches a method of detection of S. African HIV-1 subtypes by PCR and hybridization. Engelbrecht teaches using PCR

with env primer pairs. HIV-1 samples from patients with AIDS or ACR were analyzed. The env gene of 22 virus strains was sequences. Engelbrecht teaches primer pairs for env region, namely SK68 /Sk69. The PCR products were detected by probe hybridization (page 395). Hybridization with DIG oligonucleotide labeled probes was carried out on filters. Engelbrecht teaches "with the env primer pair, profile d detected 100 proviral genome copies but failed to detect many of the C-subtypes and one B-subtype" (page 397). As seen in Figure 1, the fragment sizes range from 104-592 (limitations of Claim 2). The oligo probe (SK70) used, belongs to subtype B, with ensuing weak hybridization reactions with lo level subtype C amplicons (page 397).

While Claim 1 states that the amplification product is indicative of one of four HIV-1 substypes, it is unclear how this limitation contributes to the active process of amplification and detection. Moreover, the terminal region of the amplification product is, inherently, 1-30 nucleotides in length. The claim does not appear to require any particular limitations for this terminal region. Moreover, at this region, variation between the subtypes exists, therefore, the terminal region would differ.

Engelbrecht does not specifically teach using nested primers for detection.

However, Zazzi et al. (herein referred to as Zazzi) teaches nested PCR for detection of HIV-I DNA in clinical specimens. Zazzi teaches a highly sensitive two-step PCR method was evaluated for detection of HIV-1. The product resulting from the first amplification reaction is used as the template for the second PCR with an internal (nested) primer pair. Zazzi teahes that the two step amplification protocol is simple and rapid and fulfills the requirements of sensitivity and specificity for use in a clinical laboratory (abstract).

Therefore, it would have been prima facie obvious to one of ordinary skill at the time the invention was made to have modified the PCR method of Engelbrecht to include nested PCR for the expected benefits taught by Zazzi. Zazzi specifically teaches the benefits of the nested or two step amplification over single amplification. The ordinary artisan would have been motivated to have modified the method to obtain a more sensitive and specific method using nested PCR as taught by Zazzi.

Allowable Subject Matter

15. A search of the art fails to identify a sequence from subtype B which comprises both SEQ ID NO: 20 and 28 such that it would be obvious to use the primer pair of a nucleic acid consisting of SEQ ID NO: 20 and 28 to identify subtype B. While the art teaches HIV-1 sequences comprising SEQ ID NO: 28, the art does not teach these sequences are HIV-1 subtype B, therefore, there would be no motivation to use a primer consisting of SEQ ID NO: 28 in combination with a primer consisting of SEQ ID NO: 20.

16. Claim 11 and Claim 19 both contain a primer pair comprising SEQ ID NO: 28 and 20. Claims 11 and 19 are free of the art.

Conclusion

17. Claims 11 and 19 are allowable.

18. Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

19. The art made of record and not relied upon is considered pertinent to applicant's disclosure.

A) Delwart et al. (Methods : A companion to Methods in Enzymology, Vol. 12, pages 348-354, 1997) teaches amplifying HIV using ED7 primer (page 350) which is SEQ ID NO: 20.

B) Hahn (US Pat. 6,492,110, December 10, 2002) teaches an alignment of various HIV-1 subtypes and methods of distinguishing HIV-1 subtypes.

C) Gonzalez-Villasenor (Mol. And Cell. Probes, Vol. 14, pages 137-147, July 2000) teaches a solid phase plate assay for HIV-1 genotyping subtypes. It is noted that the availability of this paper is after the international filing date of June 16, 2000.

D) Klein (WO 00/44935, August 2000) teaches multiplex real-time PCR for amplifying multiple isolates in a single sample. It is noted that this art is not prior art.

20. Any inquiry concerning this communication or earlier communications from the examiner should be directed to examiner Jeanine Goldberg whose telephone number is (571) 272-0743. The examiner can normally be reached Monday-Friday from 7:00 a.m. to 4:00 p.m.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Gary Jones, can be reached on (571) 272- 0745.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

The Central Fax Number for official correspondence is (571) 273-8300.

J. Goldberg

Jeanine Goldberg
Patent Examiner
January 31, 2005